REMARKS

Prior to the present response, original claims 3-22, 30, 31, 33, 35, 37 and 39-45 were cancelled. In the present response, claims 1, 24-29, 32, 34 and 36 have been amended; claims 23 and 46-64 have been cancelled; and claims 65-77 have been added. Accordingly, claims 1, 2, 24-29, 32, 34, 36, 38 and 65-77 are pending. Reconsideration of the rejections made in the office action of July 19, 2006 is respectfully requested.

Amendments to specification and claims:

The specification has been amended by adding the word "about" to the fifth line of the last paragraph on page 10 before "0.8 μg/ml." Literal support for this amendment is found in original claim 19 in the application as filed.

Claim 1 has been amended to eliminate the possibility of administering antibiotic tetracycline compounds. As amended, claim 1 recites administration solely of non-antibiotic tetracycline compounds.

Claim 1 has also been amended, as have several dependent claims, explicitly to recite a pharmaceutically acceptable salt of the tetracycline compounds. The tetracycline compounds used in the methods of the invention are defined as including pharmaceutically acceptable salts in the specification at, for example, page 11, lines 16-30.

Claim 24 has been amended by making it an independent claim, instead of a claim that depends from claim 1. The scope of claim 24 is not affected by the amendment.

The dependency of claims 25-29 has been changed from claim 23 (presently cancelled) to currently pending independent claim 1.

Claim 36 has been amended to define the administration of 6-demethyl-6-deoxy-4-de(dimethylamino)tetracycline as systemic administration. Claim 38, which depends from claim 36, has been amended to define the systemic administration as oral administration.

The new claims

New claim 65 limits the humans of claim 36 to humans who have skin lesions associated with acne. Support is found at page 6, lines 28-30 of the specification. ("The present invention provides methods of treating acne. As used herein, the term "acne" is a disorder of the skin characterized by... skin lesions.")

Claim 66 limits the lesions of claim 65 to pustules, papules, cysts, nodules, or comedones. Literal support for this limitation is found at page 6, lines 29 and 30.

Claim 67 further limits the lesions of claim 65 to pustules and papules. Literal support is found in the specification as in claim 66.

Claim 68 limits the lesions of claim 65 to comedones. Literal support is found in the specification as in claim 66 as well as on page 7, lines 6-8.

Claim 69 is limited to a method for treating acne rosacea, *i.e.*, rosacea. Literal support is found in the specification in original claim 2, line 1 as well as on page 7, line 3.

Claim 70 is limited to a method for treating acne vulgaris. Literal support is found in the specification in original claim 2, line 1, as well as on page 6, line 35.

Claim 71 limits the administration recited in claim 69 or 70 to administration by sustained release. Literal support is found in the specification in the paragraph bridging pages 15 and 16.

Claim 72 limits the administration recited in Claim 69 to once a day. Literal support is found in the specification on page 15, lines 19-21.

Claim 73 limits the amount of tetracycline recited in Claim 69 to an amount that results in no reduction in skin microflora during a six month treatment. Support is found in the specification on page 34, lines 25-28.

New independent claim 74 recites the same method of treating acne as in claim 1, except that the tetracycline compound is defined as a tetracycline compound wherein a substituent at any of positions 1-4 and 10-12 of the tetracycline compound or pharmaceutically acceptable salt thereof has been replaced, and wherein the resulting compound or salt has substantially less or effectively no antibiotic activity. Support is found in the specification at page 17, lines 2-4.

New claim 75 limits the tetracycline compound of claim 74 to 6-demethyl-6-deoxy-4-de(dimethylamino)tetracycline (CMT-3). Support for CMT-3 is found in the specification at page 8, lines 8 and 9.

New independent claim 76 recites the same method of treating acne as in claim 1, except that the tetracycline is in a pharmaceutical preparation that does not also comprise a bisphosphonate compound. Literal support for pharmaceutical preparations is found a page 14, lines 25-29. The omission of a bisphosphonate compound from the pharmaceutical preparation is supported in the application in the paragraph bridging pages 13 and 14. (If the tetracycline compound used in the claimed method is administered in a pharmaceutical preparation, and the method precludes administration of a bisphosphonate, it necessarily follows that the preparation cannot contain a bisphosphonate.)

New claim 77 recites a combination of the subject matter of claims 36, 38 and 65.

The Rejections

The examiner rejected the pending claims in her office action of July 19, 2006 for the following reasons:

(i) Claims 1, 2, 23-29, 32, 34, 36, 38 and 46-64 were rejected for non-statutory double patenting over co-pending application no. 10/117,709, co-pending application no. 11/061,866, and U.S. patent 7,014,858;

(ii) Claims 1, 2, 38 and 46-64 were rejected as being obvious under 35 U.S.C. 103(a) over *Arbiser* (U.S. Patent No. 6,673,843) in view of *Webster et al.*, Antimicrobial Agents and Chemotherapy 21, 770-772 (1982) or *Plewig et al.*, "Acne," Springer-Verlag, pages 261 and 297-301, New York, Heidelberg, Berlin, 1975;

(iii) Claims 1, 2, 23-29, 32, 34 and 38 were rejected as being obvious under 35 U.S.C. 103(a) over *Arbiser*, in view of *Webster et al.*, or *Plewig et al.*, as in rejection (ii), and, in addition, *McNamara et al.*, U.S. Patent No. 4,704,383; and

(iv) Claim 36 was rejected as being obvious under 35 U.S.C. 103(a) over *Arbiser*, in view of *Ramamurthy et al.*, U.S. Patent No. 5,998,390.

Rebuttal of Rejections

Applicant submits herewith a terminal disclaimer with respect to the cited applications and patent, all of which are co-owned, thereby overcoming the non-statutory double patenting rejection. Accordingly, the examiner is respectfully requested to withdraw rejection (i).

Applicant believes obviousness rejection (ii) was related to the possibility of antibiotic tetracyclines in claim 1 (and its dependent claims 2 and 38) prior to the present amendment, and

the recitation of antibiotic tetracyclines in claims 46-64. Claim 1 has presently been amended to limit the tetracycline compounds to non-antibiotic tetracycline compounds. Claims 46-64 have been cancelled. Accordingly, applicant believes obviousness rejection (ii) is moot, and respectfully requests withdrawal of obviousness rejection (ii).

Applicant respectfully rebuts obviousness rejections (iii) and (iv) for the reasons below.

The Presently Claimed Invention

The invention is directed to a method for treating acne by administering tetracycline compounds systemically, *e.g.*, orally or intravenously. The claims have been amended to limit the tetracycline compounds to those that are non-antibiotic.

It was known before the present invention that antibiotic tetracyclines were useful for treating acne, including acne rosacea. As was discussed in some detail in the background section of the specification, it was also known that the tetracyclines had beneficial properties other than their ability to inhibit bacterial growth. These beneficial properties include anti-inflammatory properties. See page 3, line 1 *et seq.* of the specification.

It was not known before the present invention, however, that the anti-inflammatory properties of tetracyclines could be exploited for treating acne in the absence of their antibiotic properties. More specifically, it was not known before the present invention that systemically administered non-antibiotic tetracyclines could be used to treat acne. Methods of treating acne, including acne rosacea, with such systemically administered non-antibiotic tetracyclines were first disclosed in the provisional application from which the present application asserts priority, and constitute the subject matter of the present claims.

The advantages of administering non-antibiotic tetracyclines are readily apparent. Non-antibiotic tetracyclines enable long term treatment of chronic diseases without the well-known disadvantages of antibiotic therapy, which include overgrowth of fungi and bacterial resistance.

The Primary Reference, *Arbiser*

The primary reference cited against the present claims in rejections (iii) and (iv) is *Arbiser*. *Arbiser* alleges the use of inhibitors of angiogenesis to treat conditions characterized by elevated levels of basic fibroblast growth factor and angiogenesis (column 3, line 48 *et seq.*). As recognized by Examiner Tran, *Arbiser* lists various skin disorders, including acne and rosacea (column 3, line 52-62), as being among such conditions. As also recognized by Examiner Tran, useful angiogenesis inhibitors are alleged to include tetracyclines, such as minocylcine. See column 4, line 6.

***Arbiser* teaches away from oral or intravenous administration to treat skin disorders**

The examiner further characterizes *Arbiser* as teaching "a method for treating diseases or disorders of the skin such as verruca vulgaris, acne and rosacea ... comprising administering **orally or parenterally** a composition comprising an angiogenesis inhibitor..." (emphasis added). (See Office Action page 5, first paragraph.) Applicant must respectfully disagree with this assertion as it applies to skin diseases and disorders.

It is true that *Arbiser* generally discloses topical, localized, or systemic administration (column 6, line 67). Systemic administration is said to be either parenteral or enteral (column 7, lines 21 and 22), including oral (column 7, line 32).

However, the different types of administration apply to specific diseases and disorders. *Arbiser* makes clear that systemic administration does not apply to skin disorders.

In particular, in the "Methods of Treatment" section of *Arbiser*, treatments of skin disorders are described as follows:

> For the treatment of skin disorders, the angiogenesis inhibitors are administered topically or regionally.

See column 8, lines 18-20.

In other words, *Arbiser* only discloses **topical or regional administration** of angiogenesis inhibitors for the treatment of skin disorders, such as acne and rosacea. There is no suggestion whatsoever in *Arbiser* that skin disorders may be treated systemically, *e.g.*, orally or intravenously.

The pending claims, by contrast, recite **oral or intravenous** administration of tetracyclines for treating acne. The disclosure in *Arbiser* of topically administered tetracyclines does not suggest orally and/or intravenously administered tetracyclines.

Quite the contrary. In fact, *Arbiser* teaches away from oral administration of angiogenesis inhibitors for the treatment of skin disorders. *Arbiser* recognizes the possibility of oral administration for certain conditions, such as for disorders of the gastrointestinal tract (column 8, lines 34-35). For skin disorders, however, *Arbiser* discloses **only** topical or regional administration.

Therefore, a person of ordinary skill in the art would understand that *Arbiser* excluded the possibility of systemic administration for acne and rosacea. Such exclusion clearly constitutes a teaching away from the claimed element of oral or intravenous administration.

The examiner recognized that *Arbiser* does not teach oral or intravenous administration to treat skin disorders during prosecution of related application serial no. 10/117,709

The examiner has previously acknowledged that *Arbiser* does not teach oral or intravenous administration of a tetracycline compound to treat skin conditions. In particular, in the November 30, 2006 Notice of Allowability issued for co-pending U.S. application no. 10/117,709, the examiner stated as the reasons for allowance:

> The closest prior art, Arbiser recognizes the possibility of oral administration of a tetracycline compound for certain conditions such as disorders of the GI tract. However, *Arbiser* does <u>not</u> teach oral or intravenous administration of a tetracycline compound in a sub-

> antimicrobial amount for the treatment of skin disorders. At column 8, lines 18-20, *Arbiser* teaches skin disorders are treated by administering the angiogenesis inhibitors topically or locally. (Emphasis added.)

See page 3, penultimate paragraph, of Notice of Allowability.

Thus, the principal reason given by the examiner for allowance of the co-pending application was that *Arbiser* does not teach oral or intravenous administration to treat skin disorders. The examiner appears to agree with applicant's position that *Arbiser* teaches away from such oral or intravenous administration.

Accordingly, the examiner has clearly acknowledged that the primary reference fails to teach the element of the claimed invention that the office action asserts is taught by the reference. In such a case, secondary references, in combination with the primary reference or by themselves, cannot support the obviousness rejections. Therefore, rejections (iii) and (iv) are not viable, and applicant respectfully requests that they be withdrawn

Nevertheless, a brief review of the secondary references is provided to emphasize that they cannot, in combination with the primary reference or by themselves, support rejections (iii) or (iv).

***Webster* and *Plewig* as secondary references**

During prosecution of related application serial no. 10/117,709, the applicant argued that neither *Webster* nor *Plewig* disclosed or suggested administration of a sub-antibacterial dose of a tetracycline compound to treat acne. In fact, it was pointed out that Plewig stresses "... that it is the antibiotic activity of antibiotics that accounts for therapeutic benefits," thereby teaching away from administration of a tetracycline other than an antibiotic dose of an antibiotic tetracycline. See applicant's July 19, 2006 office action at page 21, last paragraph.

The arguments in favor of these propositions in applicant's July 19, 2006 office action at pages 14 to 22 apply to the present claims, and are incorporated herein by reference. The examiner is encouraged to review these arguments in connection with the present application.

Webster and *Plewig*, which emphasize the importance of the antibiotic effect of tetracyclines to treat skin conditions, do not suggest the claimed invention. Nor do *Webster* and *Plewig* rectify the deficiency of the primary reference, *Arbiser*.

***McNamara* as secondary reference**

McNamara teaches administration of non-antibiotic tetracyclines for various diseases and conditions, *viz.*, periodontal diseases, corneal ulcers, bone deficiency disorders, and rheumatoid arthritis. See the abstact.

McNamara cannot, however, rectify the deficiency of *Arbiser*, because *McNamara* has the very same deficiency. It is true that *McNamara*, as *Arbiser*, generally discloses systemic administration of tetracyclines. However, for skin conditions, such as decubitus ulcers, diabetic ulcers, epidermolysis bullosa, *McNamara*, as *Arbiser*, specifies topical administration. See column 3, lines 23-28, of *McNamara*.

***Ramamurthy* as secondary reference**

A fourth secondary reference was cited in rejection (iv), which pertains only to claim 36. Claim 36 recites 6-demethyl-6-deoxy-4-de(dimethylamino)tetracycline to treat acne.

Ramamurthy teaches the inhibition of the production and activity of proteinases by the administration of a synergistic combination of a tetracycline and a bisphosphonate. Acne is mentioned as being a proteinase-dependent condition. (See col. 7, lines 45-58.)

Ramamurthy discloses administration of a **combination** of a tetracycline compound and a bisphosphonate, and preferably a synergistic combination, to inhibit excess proteinase activity. The combination is emphasized at, for example, column 5, lines 23-24; column 5 , lines 55 and 56; column 7, lines 59-61; column 8, lines 30 and 31; and column 9 , lines 60-63.

There is no suggestion in *Ramamurthy* that tetracyclines can be administered in the absence of a bisphosphonate. Therefore, a person of ordinary skill in the art would understand that *Ramamurthy* taught away from administration of a tetracycline without administering a bisphosphonate.

The present claims are directed to methods of treating acne by administering a tetracycline in the absence of a bisphosphonate. *Ramamurthy* not only does not disclose such methods, it actually teaches away from them.

Claim 36 recites administering 6-demethyl-6-deoxy-4-de(dimethylamino)tetracycline to treat acne in the absence of bisphosphonates. Therefore, *Ramamurthy* not only does not suggest the present invention, but teaches away from the invention.

In summary, *Arbiser* teaches away from systemic administration of tetracycline compounds for the treatment of acne. *Ramamurthy* teaches away from the use of tetracycline compounds in the absence of a bisphosphonate in treating acne. A primary reference that teaches away from an invention in a in view of a secondary reference that also teaches away from the invention cannot render the invention obvious.

Conclusion of Argument Based on Prior Art

The primary reference in all of the art rejections, *Arbiser*, teaches away from oral or intravenous administration of tetracycline compounds to treat skin conditions. Related claims in serial no. 10/117,709 were deemed to be allowable by Examiner Tran for this very reason.

Moreover, even if one considers the secondary references, none rectifies the deficiency of *Arbiser*. In particular, *Webster* does not suggest sub-antibiotic doses of tetracyclines to treat acne. *Plewig* teaches away from administration of non-antibiotic tetracyclines. *McNamara*, as *Arbiser*, teaches away from oral administration of tetracyclines for treatment of skin conditions. *Ramamurthy* explicitly states that administration of tetracycline compounds without administering a bisphosphonate will not be effective in treating acne, thereby also teaching away from the present invention.

Accordingly, the pending claims are not rendered obvious over the art cited in the office action. Withdrawal of rejections (i) – (iv) in the office action over the art of record is respectfully requested.

Secondary Considerations

There is further evidence to support applicant's position that the prior art neither discloses nor suggests the use of systemically administered non-antibiotic tetracyclines to treat acne, as presently claimed. In particular, the secondary references cited by the examiner have been published for many years. The *Webster* article bears a publication date of May, 1982, *i.e.*, nineteen years before the April 5, 2001 filing date of the priority date asserted by the present application. *Plewig* bears a publication date of 1975, *i.e.*, twenty-six years before the priority date asserted by the present application. McNamara was issued on November 3, 1987, *i.e.*, fourteen years before the priority date asserted by the present application.

If the secondary references rendered obvious the use of non-antibiotic tetracyclines to treat acne, surely someone would have done so in the many years since these references were published. It is significant, therefore, that no one has.

New antibiotic tetracycline product for acne currently on the market, Solodyn™

Even more significantly, a tetracycline product brought to market as recently as June of 2006 is specifically marketed as an antibiotic. A description of the product, which is called

Solodyn™, is attached hereto as exhibit A (NDA 50-808). (The page numbers are in the upper left corner of most pages, and start with page 4.) That NDA 50-808 is the new drug application for Solodyn™ can be seen from the table of the Center for Drug Evaluation and Research (CDER) of the United States Food and Drug Administration (FDA) entitled "CDER Drug and Biologic Approvals for Calendar Tear 2006 Updated through July 31, 2006." The table is attached as exhibit B.

The product, which is called Solodyn™, is described on page 4 of exhibit A as tablets of minocycline hydrochloride for oral administration to treat acne. Each tablet is reported to contain the equivalent of 45, 90, or 135 mg of the antibiotic tetracycline derivative, minocycline.

The dose of Solodyn™ is described on page 14 of the product description. Solodyn™ is said to be "... a once-daily tablet to be prescribed based on the patient's weight to achieve approximately a 1 mg/kg dosage without any loading dose."

It is clear from NDA 50-808 that Solodyn™ is administered at an antibiotic dose. For example, the product description rhetorically asks: "What is Solodyn™?" The answer provided is "... a tetracycline-class **antibiotic medicine** that contains minocycline" (emphasis added). See page 16.

If it had been obvious from the prior art that acne could be treated with a non-antibiotic tetracycline, one would have expected that the developers of Solodyn™ would have attempted to avoid the known disadvantages of administering an antibiotic dose of minocycline. Nevertheless, nineteen years after *Webster*, twenty-six years after *Plewig*, and fourteen years after *McNamara*, a new tetracycline product to treat acne is approved for administration **at an antibiotic dose**. This failure of everyone, including the developers of Solodyn™, to recognize for so long that the known therapeutic advantages of tetracyclines in the treatment of acne could be sustained, while the known disadvantages of administering an antibiotic dose of a tetracycline could be avoided, constitutes powerful evidence that it cannot have been obvious to administer a non-antibiotic tetracycline to treat acne.

***Bikowski* 2003**

In addition, a physician, Joseph B. Bikowski, MD, published an article in 2003 entitled "Subantimicrobial Dose Doxycyline for Acne and Rosacea," SKINmed 2, 234-245 (July-August 2003). The 2003 *Bikowski* article is attached as exhibit C.

The article provides important evidence that, as of the April 5, 2001 priority date of the present application, the use of non-antibiotic tetracyclines for acne and rosacea was not known. Applicant, as a matter of full disclosure, informs the examiner that Dr. Bikowski is a consultant to the assignee, CollaGenex Pharmaceuticals, Inc.

The article begins by discussing the pathogenesis of acne and rosacea, and the therapies commonly used to treat these conditions. With regard to the mechanism of action of antimicrobials in acne, Dr. Bikowski states the following:

> The multifactorial nature of acne ideally requires an agent with a variety of mechanisms exerting an effect not only on the bacteria but also on the inflammatory host response induced by the bacteria.

See page 235, column 2, second paragraph (the numbers are embedded in the text of the publisher's notice at the lower right hand corner (odd-numbers) or left hand corner (even numbers) of the pages. Accordingly, the state of the art in 2003 was the same before the April 1, 2001 priority date of the present application, namely that tetracyclines had been used for a combination of antibacterial and non-antibacterial effects.

Dr. Bikowski summarizes prior art studies that were designed to measure the efficacy of tetracyclines to treat acne in Tables I and II. In all cases, an antibacterial dose was used.

Prior art studies involving the use of tetracyclines to treat rosacea are summarized in Table III. For all cases in which the dose was revealed, an antibacterial dose was used.

Dr. Bikowski recognizes the problem of bacterial resistance that may arise during long term treatment with antibacterial compounds. He then speculates as follows:

> The exploitation of the anti-inflammatory properties of certain antibiotics **might be** sufficient to elicit a meaningful clinical response, and the administration of SD (subantibacterial doses) **may** provide effective therapy without the risk of soliciting alterations in microbial susceptibility (emphasis added). See page 236, column 2, the last full paragraph.

Bikowski further reports that the first double-blind, placebo-controlled, long-term clinical trial for the use of sub-antibacterial dose of doxycycline in acne was conducted by Skidmore and reported in an article in 2003. He then reports his own clinical trial for sub-antibacterial doses of doxycycline in adult rosacea. He reports that the clinical efficacy with sub-antibacterial doxycycline was very similar to results seen with standard doses of tetracyclines.

The speculation regarding possible future use of non-antibacterial doses of tetracyclines, and the reports of first clinical trials in 2003 is significant. The *Bikowski* article constitutes further confirmation that the state of the art before the present invention was to use tetracyclines for their combination of antibacterial and non-antibacterial effects at antibiotic doses. The first disclosure of the use of non-antibiotic tetracyclines to treat acne and rosacea was in provisional U.S. patent application no. 60/281,916 filed April 5, 2001, the priority date of which is asserted in the present application.

If the examiner believes a conversation with applicant's representative would be helpful, she is cordially invited to call him at the telephone number provided below.

Respectfully submitted,

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